JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 1991, p. 328–332
0095-1137/91/020328-05$02.00/0
Copyright © 1991, American Society for Microbiology
Vol. 29, No. 2

Effect of Hydrogen Peroxide on Growth of *Candida*, *Cryptococcus*, and Other Yeasts in Simulated Blood Culture Bottles

TONG HUAHUA, JEFFREY RUDY,† AND CALVIN M. KUNIN*
Department of Internal Medicine, The Ohio State University, Columbus, Ohio 43210

Received 16 July 1990/Accepted 8 November 1990

The addition of hydrogen peroxide to blood contained in liquid culture medium increased the dissolved-O_2 partial pressure in direct proportion to the volume injected. The effect of hydrogen peroxide on the growth of subcultured clinical isolates of *Candida albicans*, *Cryptococcus neoformans*, *Torulopsis glabrata*, and other yeasts and on the growth of blood culture isolates of representative pathogenic bacteria was compared with its effect on their growth in vented and unvented stationary bottles. *C. albicans* and *C. neoformans* grew significantly better in bottles to which hydrogen peroxide had been added than in vented or unvented bottles. The advantage of hydrogen peroxide over venting was most marked with several slowly growing strains. Similar results were obtained in shaker cultures with strains of *C. albicans* which were inoculated directly from positive blood cultures. The effect of hydrogen peroxide tended to diminish during serial passage. *T. glabrata* grew less well when hydrogen peroxide was added, perhaps because of the absence of oxidase. The growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* was not significantly inhibited or augmented by the addition of hydrogen peroxide. The growth of *Escherichia coli* was inhibited slightly. The value of the addition of hydrogen peroxide to blood cultures to improve the isolation of yeasts needs to be established by a clinical trial which would compare this method with established methods.

Disseminated candidiasis is a major cause of morbidity and mortality in patients with neutropenia, hematologic malignancies, long-term indwelling intravascular devices, and intensive antimicrobial therapy (4–6, 9, 26). The frequency of infections with *Cryptococcus neoformans* has increased in immunocompromised patients, particularly those with AIDS (10). Antemortem blood cultures may be negative in patients found at autopsy to have deep-seated candidiasis (23).

Several methods have been devised to improve the isolation of *Candida*, *Cryptococcus*, and other yeasts from the blood. These include the venting and shaking of blood culture bottles to improve oxygenation (11, 13, 16, 18–21, 23–25), improving the growth media (18), and using biphasic culture systems (2, 17), radiometric methods (3, 16, 17, 24, 25), and lysis-centrifugation (1, 3, 7). Nonculture methods have also been introduced to improve the diagnosis (15, 27).

We have devised a method for delivering high concentrations of oxygen to closed liquid blood culture systems by adding hydrogen peroxide. Catalase, which is present in erythrocytes, rapidly breaks down the hydrogen peroxide to oxygen and water. The hemoglobin becomes oxygenated and may serve as a continuous source of oxygen. This report describes the enhanced growth of some clinical isolates of *C. albicans* and *C. neoformans* but not of *Torulopsis glabrata* or other yeasts by the addition of hydrogen peroxide to simulated blood culture bottles.

MATERIALS AND METHODS

Microorganisms. Blood culture isolates of *C. albicans*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* were obtained from the Ohio State University Hospitals. *C. neoformans*, *T. glabrata*, and other yeasts were isolated from a variety of sources, including blood, cerebrospinal fluid, and urine. The initial studies were conducted with strains which had been passaged several times on solid media. These strains were subcultured on sheep blood agar plates. A single colony was transferred to Trypticase soy broth and incubated overnight at 37°C. In subsequent studies, yeasts were subcultured directly, without passage, from positive clinical blood culture bottles into the simulated blood culture system.

Simulated blood culture methods. Five-milliliter samples of human blood were added to replicate bottles which contained 50 ml of BBL brain heart infusion broth with *p*-aminobenzoate, CO_2, and SPS (Becton Dickinson Microbiology Systems, Cockeysville, Md.). One bottle was left unvented, one was vented continuously with an ECB vent subunit (Difco Laboratories, Detroit, Mich.), and one received hydrogen peroxide. Fresh blood used in the initial experiments was obtained from volunteers; thereafter, outdated American Red Cross blood was used. The inoculum size for subcultured strains was estimated by using McFarland standards and confirmed by plating serial dilutions. The inoculum size for strains isolated directly from positive blood cultures was estimated by Gram stain and confirmed by plating serial dilutions. It was found that one colony per high-power field (magnification, ×1,000) was equivalent to about 10^5 CFU/ml. Two sets of inocula differing by 10-fold were used in each experiment. Results are reported for bottles which contained inocula of 50 CFU or less. Hydrogen peroxide was added as 1 ml of a 3% solution (Cumberland-Swan, Inc., Smyrna, Tenn.) except where stated otherwise. A fresh bottle was used in each experiment. Partial O_2 pressure (pO_2) in blood culture bottles was measured with a Blood Microsystem (BMS 3, MK2; Radiometer, Copenhagen, Denmark). The microorganisms were added immediately after the hydrogen peroxide unless stated otherwise. The bottles were incubated as stationary cultures or were shaken at 100 cycles/min in a Versa Bath (model 236; Fisher, Malvern, Pa.) at 30 to 32°C. Aliquots were subcul-

* Corresponding author.
† Present address: G. H. Besselaar Associates, Princeton, NJ 08640-6681.

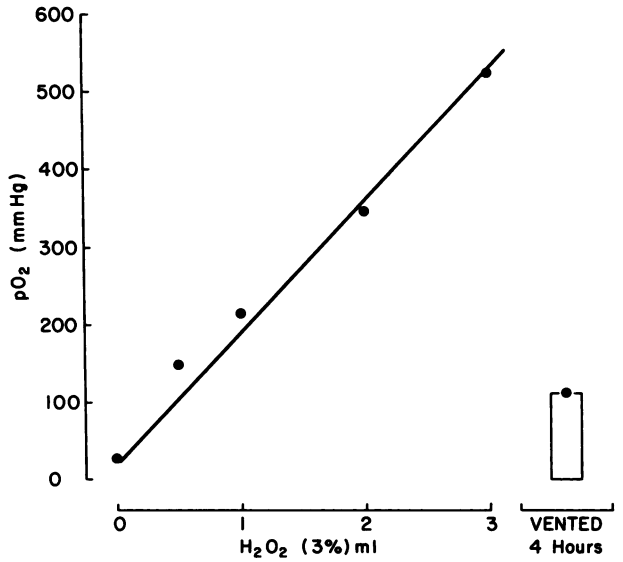

FIG. 1. Effect of the addition of hydrogen peroxide on the pO_2 (dissolved oxygen) in simulated blood culture bottles in which 5 ml of human blood was added to 50 ml of medium.

tured by serial dilution onto Trypticase soy agar plates at 12, 24, 48, and 72 h. Colonies were counted after 48 h of incubation at 30 to 32°C. Catalase activity was determined by the direct addition of hydrogen peroxide to colonies. Tetramethyl-*p*-phenylalanine reagent (Marion Scientific, Kansas City, Mo.) was used to test for oxidase. Statistical analysis was conducted by using Wilcoxon's signed rank test (12).

RESULTS

Concentrations of oxygen obtained after addition of hydrogen peroxide to blood culture bottles. There was a rapid evolution of gas and an immediate change of color from dark to bright red after hydrogen peroxide was added to bottles containing blood. The bubbles soon disappeared, but the blood remained bright red for several weeks. Measurements of the pO_2 in the media of bottles which were unvented, which were vented for 4 h, and to which hydrogen peroxide had been added are shown in Fig. 1. There was a linear relation between the volume of hydrogen peroxide added and the pO_2. The pO_2 in vented bottles was about the same as that obtained with 0.5 ml of hydrogen peroxide.

Effects of volume and timing of addition of hydrogen peroxide and the source of human blood on growth of yeasts and bacteria in simulated blood culture bottles. Preliminary studies were conducted to determine the optimal conditions for the growth of the microorganisms. A volume of 1 or 2 ml of hydrogen peroxide was found to be about equally effective in enhancing the growth of *C. albicans* and *C. neoformans* and did not significantly inhibit the growth of the bacteria. For example, at 24 h of incubation, in simulated blood culture bottles containing 1 or 2 ml of hydrogen peroxide, the mean concentrations of eight strains of *C. albicans* were 1.2×10^6 and 1.5×10^6 CFU/ml, respectively, and the mean concentrations of 11 strains of *C. neoformans* were 236 and 175 CFU/ml, respectively. Smaller volumes (0.5 ml) of hydrogen peroxide were not as effective. Larger volumes (3 or 4 ml) reduced growth by about half.

The growth of clinical isolates of *S. aureus*, *P. aeruginosa*, and *E. faecalis* was not inhibited or enhanced by the addition of 1 or 2 ml of hydrogen peroxide. A strain of *E. coli* was inhibited by the addition of hydrogen peroxide by about a factor of 1 $\log_{10}$. Nevertheless, the growth of this organism was rapid in the presence of hydrogen peroxide. For example, after 12 h, an inoculum of 52 CFU of *E. coli* reached a concentration of 10^6 CFU/ml in the presence of hydrogen peroxide compared with 10^7 CFU/ml in the absence of hydrogen peroxide.

There was no difference in the growth of the yeasts or bacteria when hydrogen peroxide was added either immediately before or after the blood was added. The microorganisms grew, with or without hydrogen peroxide, in outdated Red Cross blood just as well as in fresh human blood.

TABLE 1. Growth of 14 blood culture isolates of *C. albicans* in stationary simulated blood culture bottles[a]

Inoculum (CFU)	Concn (CFU/ml) of 24-h subcultures			Concn with H_2O_2/concn in vented bottles
	In unvented bottles	In vented bottles	With H_2O_2[b]	
25	17	3,000	260,000	86.7
6	25	2,700	290,000	107.4
8	60	60,000	16,000	0.3[c]
3	570	16,550	760,000	45.9
8	30,000	210,000	820,000	3.9
1	260	94,000	767,000	8.2
18	15,500	292,500	654,500	2.2
13	8,500	160,000	600,000	3.8
9	620,000	1,400,000	1,100,000	0.8
19	3	10	34	3.4[d]
5	67,000	640,000	750,000	1.2
18	430,000	1,600,000	2,000,000	1.3
10	450,000	770,000	790,000	1.0
14	2,600,000	4,500,000	4,100,000	0.9

[a] For all isolates, growth in vented bottles and in bottles with H_2O_2 was greater than growth in unvented bottles ($P < 0.01$ by Wilcoxon's signed rank test). Growth in bottles with H_2O_2 was greater than growth in vented bottles for 10 isolates (71.4%) ($P < 0.05$).

[b] One milliliter of a 3% solution was added to each bottle.

[c] The ratio was 16.5 with an inoculum of 80 CFU.

[d] The ratio was 1.6 at 48 h.

Growth of blood isolates of *C. albicans* in unvented, vented, and hydrogen peroxide-containing blood culture bottles. Fourteen strains of *C. albicans* were added to replicate stationary simulated blood culture bottles. Growth was determined at 12, 24 and 48 h. The findings with small inocula at 24 h are shown in Table 1. Similar results were obtained with 10-fold-higher inocula. All strains grew better in vented bottles and in those with hydrogen peroxide than in unvented bottles (Table 1). Most strains grew better in hydrogen peroxide-containing bottles than in vented bottles, but considerable variation was observed. Three strains that grew slowly (i.e., did not grow to 10^5 CFU/ml by 24 h) achieved 10-fold or greater concentrations (CFU per milliliter) in hydrogen peroxide-containing bottles than in vented bottles. The effect of hydrogen peroxide was less marked for the more rapidly growing strains. Similar results were observed at 12 h. By 48 h, virtually all the cultures had achieved full growth, and no significant differences were observed among the various culture methods.

Growth of *C. neoformans* in unvented, vented, and hydrogen peroxide-containing blood culture bottles. Fourteen strains of *C. neoformans* were added to stationary simulated blood culture bottles, and growth was determined at 24, 48,

TABLE 2. Growth of 14 isolates of *C. neoformans* in stationary simulated blood culture bottles[a]

Inoculum (CFU)[b]	Concn (CFU/ml) of 48-h subcultures			Concn with H_2O_2/concn in vented bottles
	In unvented bottles	In vented bottles	With H_2O_2[c]	
10	600	777,000	1,400,000	1.8
10	8,300	48,000	310,000	6.5
5	31,600	152,000	467,000	3.1
5	910	97,000	240,000	2.5
14	27,000	680,000	940,000	1.4
13	140,000	1,400,000	1,900,000	1.4
47	240	7,500	110,000	14.7
13	3,500	59,000	120,000	2.0
7	2,100	2,300	27,000	11.7
5	210	1,920	2,960	1.5
5	38	45	126	2.8
5	5,600	600,000	700,000	1.2
3	1,060	6,300	13,000	2.1
9	460,000	2,300,000	2,000,000	0.9

[a] Growth in vented bottles and in bottles with H_2O_2 was greater than growth in unvented bottles for all 14 isolates. Growth with H_2O_2 was greater than growth in vented bottles for 13 isolates (92.9%). (For all data, $P < 0.01$ by Wilcoxon's signed rank test.)

[b] Reading from top to bottom, four blood cultures, nine cerebrospinal fluid cultures, and one urine culture were used.

[c] One milliliter of a 3% solution was added to each bottle.

and 72 h. The cryptococci grew much more slowly than the candidas. At 24 h, the concentrations (in CFU per milliliter, with standard deviations in parentheses) were 120 (195), 163 (260.5), and 305 (308) for strains grown in unvented, vented, and hydrogen peroxide-containing bottles, respectively. The counts taken at 48 h are shown in Table 2. Growth was significantly greater in vented than in unvented bottles and was even greater in the presence of hydrogen peroxide. Similar results were obtained with 10-fold-higher inocula. The only *Cryptococcus* strain that grew about the same in hydrogen peroxide-containing bottles and in vented bottles was a rapidly growing strain isolated from urine.

Growth of *T. glabrata* and other yeasts in unvented, vented, and hydrogen peroxide-containing blood culture bottles. The growth of six strains of *T. glabrata* in stationary cultures was about the same in vented and in unvented bottles but was almost always less in bottles to which hydrogen peroxide had been added (Table 3). All of the strains of *T. glabrata* were catalase positive but oxidase negative, whereas several strains of *C. albicans* and *C. neoformans* that were tested were both catalase positive and oxidase positive. The growth

TABLE 3. Growth of clinical isolates of *T. glabrata* in stationary simulated blood culture bottles

Inoculum (CFU)[a]	Concn (10^4 CFU/ml) of subcultures			Concn with H_2O_2/concn in vented bottles
	In unvented bottles	In vented bottles	With H_2O_2[b]	
10	270	160	19	0.1
9	66	75	15	0.2
18	94	190	46	0.2
20	230	260	130	0.5
17	410	520	480	0.9
45	11	15	20	1.3

[a] Reading from top to bottom, one blood and five urine cultures.

[b] One milliliter of a 3% solution was added to each bottle.

TABLE 4. Effects of venting, addition of hydrogen peroxide, and shaking on growth of *C. albicans*[a]

Culture type and inoculum (CFU)	Mean concn (CFU/ml)		
	In unvented bottles	In vented bottles	With H_2O_2
Stationary, 17.6	1.8×10^4	2.7×10^4	1.1×10^5
Shaker, 17.6	3.3×10^5	4.5×10^5	8.0×10^5

[a] Growth at 24 h of 11 strains isolated directly from positive blood cultures in simulated culture bottles. For stationary cultures, all 11 strains grew better in vented than in unvented bottles ($P < 0.001$ by Wilcoxon's signed rank test). For shaker cultures, 7 strains (63.6%) grew better in vented than in unvented bottles ($P < 0.05$ by Wilcoxon's signed rank test). For both stationary and shaker cultures, 10 (90.9%) grew better with H_2O_2 than in unvented bottles ($P < 0.001$) and 8 (72.7%) grew better with H_2O_2 than in vented bottles ($0.05 < P < 0.10$ for stationary cultures; $P < 0.01$ for shaker cultures).

of single isolates of *Candida tropicalis*, *Candida parapsilosis*, and *Trichosporon beigelii* was not enhanced or inhibited by the addition of hydrogen peroxide.

Growth of yeasts isolated directly from positive blood cultures in unvented, vented, and hydrogen peroxide-containing blood culture bottles. In order to minimize changes in oxygen requirements which might occur during serial passage, in vitro strains of *C. albicans* were inoculated directly into the simulated blood culture system as soon as the blood culture was found to be positive in the clinical laboratory. The inoculum size was estimated by Gram stain. Several of the strains were then passaged three times on sheep blood agar plates. A single colony was picked, grown overnight in Trypticase soy broth, and added to the simulated blood culture system. Replicate bottles were kept stationary or were shaken.

Most strains of *C. albicans* isolated directly from positive blood culture bottles grew better in the presence of hydrogen peroxide than in vented or unvented bottles (Table 4). The findings for two strains that grew exceptionally well in

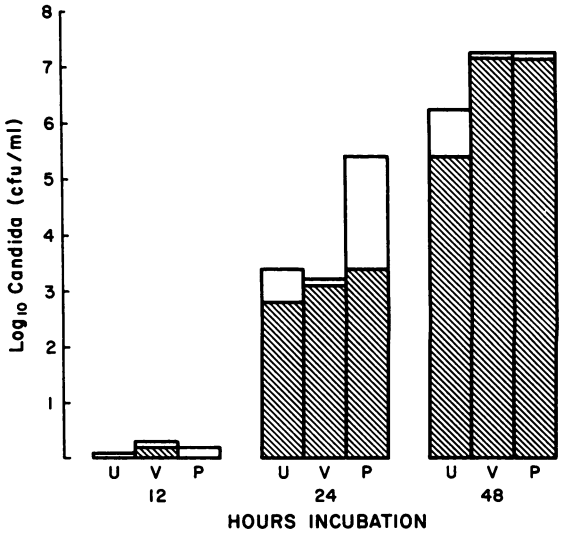

FIG. 2. Growth of *C. albicans* 6833 in a simulated blood culture system which was unvented (U) or vented (V) or to which 1 ml of 3% hydrogen peroxide (P) had been added. Growth in stationary (▨) and shaker (□) cultures is shown. This strain was inoculated directly (without passage) into the simulated blood culture system from a clinically positive blood culture bottle.

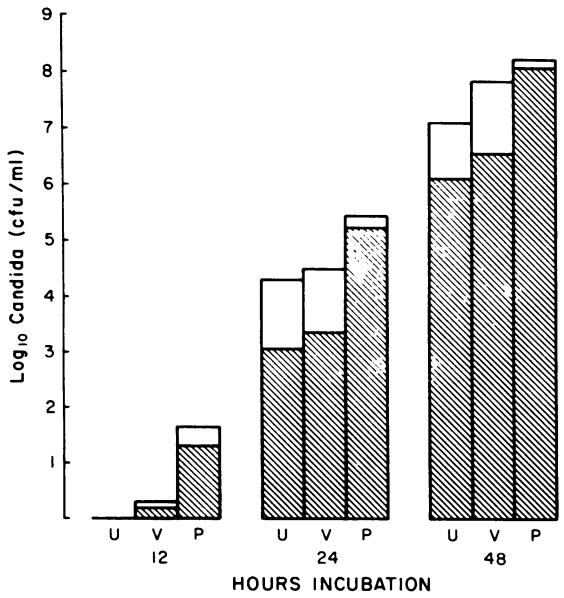

FIG. 3. Growth of *C. albicans* 8118 in a simulated blood culture system which was unvented (U) or vented (V) or to which 1 ml of 3% hydrogen peroxide (P) had been added. The conditions were the same as those described for Fig. 2.

hydrogen peroxide bottles are shown in Fig. 2 and 3. The effect of shaking was more pronounced with one of the strains. This result may have been related to differences in the relative rate of growth of the organisms. The enhancing effect of hydrogen peroxide on the growth of four of the strains tested tended to diminish after serial passage.

DISCUSSION

C. albicans has been shown to grow better in blood culture systems that are well oxygenated by ambient air (2, 11, 13, 16, 18–21, 23–25). The experiments described above were conducted to determine whether the growth of candidas and other pathogenic yeasts might be improved by the presence of even higher concentrations of oxygen. The addition of hydrogen peroxide to blood-containing culture bottles provides a simple method for increasing oxygen tension. The addition of 1 ml of a 3% solution of hydrogen peroxide to 50 ml of culture medium containing 5 ml of human blood appears to be optimal for the growth of yeasts. This addition produces a pO_2 of about 200 mm Hg (ca. 30 kPa), or about twice that achieved by venting and shaking the bottles. Hydrogen peroxide at this concentration did not interfere with or enhance significantly the growth of bacteria which are commonly isolated from the blood. The growth of *E. coli* was inhibited somewhat, but this organism grew so rapidly in the simulated blood culture system that it is doubtful that the addition of small amounts of hydrogen peroxide will interfere with the isolation of this organism from blood cultures.

Clinical isolates of *C. albicans* and *C. neoformans* which had been passaged several times in the laboratory grew significantly better in bottles to which hydrogen peroxide had been added, but the advantage of this method over venting to ambient air appeared to be small except for several slowly growing strains. Similar results were obtained for strains of *C. albicans* which were inoculated directly from positive blood cultures without passage.

Considerable variation was noted among *Candida* strains in rates of growth and the effects of venting and the addition of hydrogen peroxide to blood culture bottles. Candidas are known to be affected by the selective pressures of serial passage in laboratory media (8, 14). It is not clear whether the generation of free oxygen radicals or hydroxyl ions were limiting factors. It is possible that the organisms were protected to some extent from hydrogen peroxide and its products by their endogenous catalase, oxidase, or other cytochrome enzymes (22). This notion is supported in part by the observation that *T. glabrata*, which is oxidase negative, tended to grow less well in bottles to which hydrogen peroxide had been added.

It is possible that the growth of other slowly growing, oxygen-requiring microorganisms, such as *Mycobacterium avium-M. intracellulare*, *Mycobacterium tuberculosis*, and *Histoplasma capsulatum*, might be enhanced by the addition of hydrogen peroxide to blood culture bottles.

It is not entirely clear from these in vitro observations whether adding hydrogen peroxide will result in earlier isolation of candidas, other yeasts, and possibly fungi from blood. The growth of candidas and cryptococci should be augmented by hydrogen peroxide most in systems which are not sufficiently aerated. The ultimate value of the addition of hydrogen peroxide to blood culture systems needs to be established by controlled clinical trials in humans. These trials will require comparisons with automated systems (such as BACTEC) which are routinely flushed with oxygen, with the Isolator system, and with a vented biphasic system with and without hydrogen peroxide added.

ACKNOWLEDGMENT

We appreciate the help of Tom Clanton of the Division of Pulmonary Medicine, The Ohio State University, for assistance in measuring pO_2 in the blood culture systems.

REFERENCES

1. **Bille, J., R. S. Edson, and G. D. Roberts.** 1984. Clinical evaluation of the lysis-centrifugation blood culture system for the detection of fungemia and comparison with a conventional biphasic broth blood culture system. J. Clin. Microbiol. **19**:126–128.
2. **Bille, J., G. D. Roberts, and J. A. Washington.** 1983. Retrospective comparison of three blood culture media for the recovery of yeasts from clinical specimens. Eur. J. Clin. Microbiol. **2**:22–25.
3. **Brannon, P., and T. E. Kiehn.** 1985. Large-scale clinical comparison of the lysis-centrifugation and radiometric systems for blood culture. J. Clin. Microbiol. **22**:951–954.
4. **Brooks, R. G.** 1989. Prospective study of Candida endophthalmitis in hospitalized patients with candidemia. Arch. Intern. Med. **149**:2226–2228.
5. **Bross, J., G. H. Talbot, G. Maislin, S. Hurwitz, and B. L. Strom.** 1989. Risk factors in nosocomial candidemia: a case-control study in adults without leukemia. Am. J. Med. **87**:614–620.
6. **Bryan, C. S.** 1989. Clinical implications of positive blood cultures. Clin. Microbiol. Rev. **2**:329–353.
7. **Chan, R., R. Munro, and P. Tomlinson.** 1986. Evaluation of lysis filtration as an adjunct to conventional blood culture. J. Clin. Pathol. **39**:89–92.
8. **Dutton, S., and C. W. Penn.** 1989. Biological attributes of colony-type variants of *Candida albicans*. J. Gen. Microbiol. **135**:3363–3372.
9. **Edwards, J. E.** 1987. Severe candidal infections: clinical perspective. Ann. Intern. Med. **89**:91–106.
10. **Good, C. B., and W. A. Coax.** 1990. Cryptococcal infections in patients with AIDS. N. Engl. J. Med. **322**:701–702.
11. **Harkness, J. L., M. Hall, D. M. Ilstrup, and J. A. Washington II.** 1975. Effects of atmosphere of incubation and of routine subcultures on detection of bacteremia in vacuum blood culture bottles. J. Clin. Microbiol. **2**:296–299.

12. **Hollander, M., and D. A. Wolfe.** 1973. Nonparametric statistical methods, p. 138–144. John Wiley & Sons, Inc., New York.
13. **Jones, J. M.** 1990. Laboratory diagnosis of invasive candidiasis. Clin. Microbiol. Rev. **3**:32–45.
14. **Kennedy, M. J., A. L. Rogers, and R. J. Yancey, Jr.** 1989. Environmental alteration and phenotypic regulation of *Candida albicans* adhesion to plastic. Infect. Immun. **57**:3876–3881.
15. **Lemieux, C., G. St-Germain, J. Vincelette, L. Kaufman, and L. de Repentigny.** 1990. Collaborative evaluation of antigen detection by a commercial latex agglutination test and enzyme immunoassay in the diagnosis of invasive candidiasis. J. Clin. Microbiol. **28**:249–253.
16. **Muñoz, P., J. C. L. Bernaldo de Quirós, J. Berenguer, M. Rodríguez Créixems, J. J. Picazo, and E. Bouza.** 1990. Impact of the BACTEC NR system in detecting *Candida* fungemia. J. Clin. Microbiol. **28**:639–641.
17. **Prevost, E., and E. Bannister.** 1981. Detection of yeast septicemia by biphasic and radiometric methods. J. Clin. Microbiol. **13**:655–660.
18. **Reeder, J. C., L. A. Ganguli, D. B. Drucker, M. G. L. Keaney, and A. C. C. Gibbs.** 1989. The improved recovery of *Candida albicans* from fluid culture media. Microbios **60**:71–77.
19. **Roberts, G. D., C. Horstmeier, M. Hall, and J. A. Washington II.** 1975. Recovery of yeast from vented blood culture bottles. J. Clin. Microbiol. **2**:18–20.
20. **Roberts, G. D., and J. A. Washington II.** 1975. Detection of fungi in blood cultures. J. Clin. Microbiol. **1**:309–310.
21. **Tenney, J. H., L. B. Reller, S. Mirrett, M. P. Weinstein, and W.-L. L. Wang.** 1982. Controlled evaluation of the effect of atmosphere of incubation on detection of bacteremia and fungemia in supplemented peptone broth. J. Clin. Microbiol. **16**:437–442.
22. **Verduyn, C., M. L. F. Giuseppin, W. A. Scheffers, and J. P. van Dijken.** 1988. Hydrogen peroxide metabolism in yeasts. Appl. Environ. Microbiol. **54**:2086–2090.
23. **Washington, J. A., II (ed.).** 1978. The detection of septicemia, p. 90–99. CRC Press, Inc., Boca Raton, Fla.
24. **Weinstein, M. P., S. Mirrett, L. G. Reimer, and L. B. Reller.** 1989. Effect of agitation and terminal subcultures on yield and speed of detection of the Oxoid signal blood culture system versus the BACTEC radiometric system. J. Clin. Microbiol. **27**:427–430.
25. **Weinstein, M. P., S. Mirrett, L. G. Reimer, and L. B. Reller.** 1990. Effect of altered headspace atmosphere on yield and speed of detection of the Oxoid signal blood culture system versus the BACTEC radiometric system. J. Clin. Microbiol. **28**:795–797.
26. **Wey, S. B., M. Mori, M. A. Pfaller, R. F. Woolson, and R. P. Wenzel.** 1989. Risk factors for hospital-acquired candidemia. Arch. Intern. Med. **149**:2349–2353.
27. **Wong, B., K. L. Brauer, J. R. Clemens, and S. Beggs.** 1990. Effects of gastrointestinal candidiasis, antibiotics, dietary arabinitol, and cortisone acetate on levels of the *Candida* metabolite D-arabinitol in rat serum and urine. Infect. Immun. **58**:283–288.